Addendum to Screening for Ovarian Cancer: Evidence Update for the U.S. Preventive Services Task Force Reaffirmation Recommendation Statement

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A review of the evidence (encompassing articles published between 2002 and 2008) surrounding the benefits and harms of screening for ovarian cancer was prepared for the U.S. Preventive Services Task Force (USPSTF) in 2008. The report concluded that no substantial new evidence regarding the benefits of screening was available at that time. At the request of the USPSTF, investigators at the Oregon Evidence-based Practice Center subsequently performed a bridge search to identify any new, substantial evidence on the benefits and harms of screening for ovarian cancer in average-risk, asymptomatic women published between October 15, 2007 and July 26, 2011. The purpose of this Addendum is to present results from this bridge literature search, which, together with the 2008 report, informed the USPSTF's reaffirmation statement on screening for ovarian cancer in 2012.

This report is based on research conducted by staff at the Oregon Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. HHSA 290-2007-10057-I, Task Order No. 3). The investigators involved have declared no conflicts of interest with objectively conducting this research. The findings and conclusions in this document are those of the authors, who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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Abstract

Purpose: To conduct a bridge literature search in order to inform a reaffirmation statement on ovarian cancer screening.

Background: In 1996, the U.S. Preventive Services Task Force (USPSTF) concluded that screening asymptomatic women for ovarian cancer via ultrasonography, serum tumor markers, or pelvic examination was not recommended (D recommendation). In 2004, a brief evidence review confirmed the 1996 report; based on this, the USPSTF reissued its recommendation against routine screening (D recommendation). Specifically, while there was fair evidence that screening by cancer antigen (CA)-125 testing or transvaginal ultrasonography resulted in detection of ovarian cancer at an earlier stage, there also was fair evidence that the impact on mortality was small and that the potential harms, such as invasive diagnostic testing, might outweigh potential benefits. Subsequent to the 2004 recommendation statement, an unpublished review of the literature between July 1, 2002 and January 15, 2008 concluded that there was no new evidence regarding the benefits of screening. Additional data on harms (e.g., unnecessary surgery) associated with screening with a combination of ultrasonography and CA-125 testing were reviewed. On February 13, 2008, all Task Force members agreed that the D recommendation on screening for ovarian cancer could be affirmed.

Methods: PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched to identify new, substantial evidence on screening for ovarian cancer in average-risk, asymptomatic women published between October 15, 2007 and July 26, 2011. Searches were restricted to English-language studies in core clinical journals and focused largely on trials. Two individuals reviewed titles and abstracts to identify potentially relevant articles.

Results: Of 30 potentially relevant articles, four articles from three trials were identified for inclusion in this report. The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial found that screening with CA-125 testing and transvaginal ultrasonography did not improve cancer-specific or overall mortality compared with usual care. The PLCO Trial also confirmed the risk of potential harms associated with false-positive screening test results. Two additional randomized, controlled trials, the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) and Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS), presented screening test or screening algorithm characteristics, including potential harms due to associated complications, although neither has published results on mortality.

Conclusions: Of three randomized, controlled trials on ovarian cancer screening published during the search period, only one (PLCO Trial) published results on mortality. Those results are consistent with the current USPSTF guidelines for ovarian cancer screening among asymptomatic, average-risk women. Information from the two other trials may be useful for the USPSTF to consider in the future: SCSOCS has been completed but mortality results have not yet been published, and UKCTOCS is ongoing through the end of 2014.

Introduction

Ovarian cancer was estimated to be the ninth most common cancer and fifth most common cause of cancer-related mortality among U.S. women in 2011.[1] While 5-year survival from ovarian cancer is 94 percent when identified at the local stage, only 15 percent of ovarian tumors are diagnosed at this stage. Most (62 percent) cases of ovarian cancer are diagnosed at the distant stage, when 5-year survival is only 28 percent. Thus, screening for ovarian cancer might reduce mortality by identifying tumors at an earlier, more treatable stage. However, despite its significant disease burden, ovarian cancer is relatively rare in the general population, with an estimated age-adjusted incidence of 13 per 100,000 women.[2] The specificity of any screening strategy must therefore be high in order to achieve an acceptable positive predictive value (PPV), particularly given the invasive followup testing associated with positive screening results for ovarian cancer.

The U.S. Preventive Services Task Force (USPSTF) previously recommended against screening for ovarian cancer in the general population, in part based on a determination that potential harms might outweigh potential benefits. In 1996, the USPSTF concluded that screening asymptomatic women for ovarian cancer via ultrasonography, serum tumor markers, or pelvic examination was not recommended (D recommendation).[3] In 2004, a brief evidence review confirmed the 1996 report and recommended against routine screening (D recommendation). While there was fair evidence that screening by cancer antigen (CA)-125 testing or transvaginal ultrasonography resulted in detection of ovarian cancer at an earlier stage, there was also fair evidence that the impact on mortality was likely to be small and that the potential harms, such as invasive diagnostic testing, might outweigh the potential benefits.[4,5] Subsequent to the 2004 recommendation statement, an unpublished review of the literature reported between July 1, 2002 and January 15, 2008 concluded that there was no new evidence on the benefits of screening.[6] Additional data regarding harms (e.g., unnecessary surgery) associated with screening with a combination of ultrasonography and CA-125 testing were summarized in the report. On February 13, 2008, all Task Force members agreed that the D recommendation on screening for ovarian cancer could be affirmed, but did not issue an updated recommendation at that time.

The purpose of this Addendum is to present results from a bridge literature search to inform the 2012 USPSTF reaffirmation statement on ovarian cancer screening.

Methods

PubMed, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched to identify new, substantial evidence on ovarian cancer screening published between October 15, 2007 and July 26, 2011. Searches were restricted to English-language studies in core clinical journals and focused largely on trials following a search strategy developed by the Agency for Healthcare Research and Quality. The search strategy was modified slightly to include a wider range of studies in more recent years.

The initial literature search yielded 848 titles and/or abstracts. Two individuals reviewed titles and abstracts to identify potentially relevant articles. Thirty articles were identified as potentially eligible and reviewed in full. Of these, articles were excluded for the following (nonmutually exclusive) reasons: not related to ovarian cancer (n=1), not related to screening (n=21), did not include relevant outcomes (n=4), focused on a high-risk or special patient population (n=2), and not an appropriate study type (n=3). Thus, four articles from three studies were identified for inclusion in this report. These articles were reviewed by two individuals and are summarized below.

Results

Three randomized, controlled trials[7-9] published results on ovarian cancer screening during the period covered by this review. Only one study—the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial—presented information on mortality.[7] The other two studies[8,9] presented information on screening characteristics and harms related to false-positive screening results. Findings from the three trials are summarized below.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial

In June 2011, the PLCO Cancer Screening Trial concluded that screening women at average risk for ovarian cancer with CA-125 testing and transvaginal ultrasonography did not reduce ovarian cancer mortality compared with usual care.[7] The PLCO Trial also confirmed the potential harms associated with false-positive screening results for ovarian cancer, including a relatively high frequency of surgery and surgical complications following false-positive results. Thus, recent results from one of the few randomized trials on ovarian cancer screening are consistent with existing USPSTF recommendations.

The PLCO Trial is a randomized, controlled trial conducted in the United States to determine the impact of screening on cause-specific mortality for several types of cancer, including ovarian cancer. From 1993 to 2001, 78,216 women aged 55 to 74 years were recruited from the catchment area of 10 screening centers and randomized to receive either 1) annual screening with CA-125 testing for 6 years and transvaginal ultrasonography for 4 years or 2) usual care. After excluding women with a prior bilateral oophorectomy, 68,557 women remained in the analysis.

Women were followed until the earliest of diagnosis, death, date of last contact, fulfillment of post-randomization 13-year followup, or February 28, 2010. Median followup was 12.4 years. Cases were identified by study questionnaire, cancer registry linkage where possible, and linkages with the National Death Index. Ovarian, primary peritoneal, and fallopian tube cancer were all considered ovarian cancer cases for this study. Primary peritoneal and fallopian tube cancer comprised 20 percent of cancer cases in the intervention group and 14 percent in the control group; the statistical significance of the results remained the same when these cases were excluded. Screening-detected cancer was defined as ovarian cancer identified as a result of followup to a positive test result within 9 months of the screening test. Positive screening test results were reported to patients and their physicians for management of abnormal results. False-

positive results were cases in which a positive screening examination did not result in a cancer diagnosis; tumors of low malignant potential were considered false positives.

Among the 34,253 women in the intervention/screening group, 212 ovarian cancer cases and 118 ovarian cancer deaths were identified. Among the 34,304 women in the usual care group, there were 176 ovarian cancer cases and 100 ovarian cancer deaths. No reduction in ovarian cancer mortality was observed in the intervention group compared with those receiving usual care (relative risk [RR], 1.18 [95% CI, 0.82–1.71]), and the study was stopped early upon reaching the "boundary for futility." All-cause mortality (excluding the PLCO endpoints of ovarian, lung, and colorectal cancer) was also similar in the two randomized groups (RR, 1.01 [95% CI, 0.96–1.06]).

Stage at diagnosis was generally similar in the intervention and usual care groups, although there was a nonstatistically significant reduction in the proportion of Stage IV tumors in the intervention group (20 vs. 31 percent in the usual care group). However, the proportion of advanced tumors (Stages III and IV combined) was almost identical in the intervention and control groups (77 and 78 percent, respectively). The failure to demonstrate a stage-shift at cancer diagnosis is consistent with the lack of improved mortality among the intervention group in the trial. Study investigators evaluated screening compliance in the intervention group, contamination by screening outside the trial in the control group, and treatment of diagnosed cancers, concluding that none explained the null study findings.

Approximately one-third of women (1,080 of 3,285) with false-positive results underwent surgery (32.9 percent for oophorectomy) following a positive screening result, and 15 percent experienced at least one major complication. The most frequent complications associated with surgery were infection (40 percent of complications), direct surgical complications, or cardiovascular/pulmonary complications. Data from a supplemental questionnaire indicated that oophorectomy was significantly more likely to be reported (RR, 1.33 [95% CI, 1.24–1.43]) among women in the intervention group (7.7 percent) than women in the usual care group (5.8 percent).

Prior to publishing its mortality results, the PLCO Trial published findings from its first four rounds of screening.[10] Combined screening with CA-125 testing and transvaginal ultrasonography produced a PPV of 1.0 to 1.3 percent over the four screening cycles, with an overall ratio of surgery to screen-detected cancer of 19.5:1. Additionally, the majority (72 percent) of screen-detected cancer cases were late-stage (Stage III or IV) tumors,[10] similar to the percentage of tumors diagnosed at a regional or distant stage (79 percent) in the general U.S. population.[2]

U.K. Collaborative Trial of Ovarian Cancer Screening

The U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) is a randomized, controlled trial of 202,638 postmenopausal women aged 50 to 74 years who were recruited through 13 centers of the National Health Service in England, Wales, and Northern Ireland.[8] Between 2001 and 2005, women were randomized to one of three groups: 1) annual screening with CA-125 testing, with abnormal tests results followed up with transvaginal ultrasonography

(the multimodal screening [MMS] group), 2) annual screening with transvaginal ultrasonography (the ultrasonography screening [USS] group), or 3) no treatment. Abnormal screening test results were repeated and, if abnormality persisted, clinically evaluated and treated. Randomization was done in a 1:1:2 ratio, with 50,640 women randomized to the MMS group, 50,639 to the USS group, and 101,359 to the untreated group.

A patented ovarian cancer risk algorithm was used to assign an ovarian cancer risk score to women in the MMS group based on age and absolute CA-125 level at the first screening and CA-125 value and trajectory for subsequent screening visits. The risk score classified women as normal, intermediate, or high risk; women with normal results were not retested until the next annual screening date. Women who declined transvaginal ultrasonography were scanned with transabdominal ultrasonography instead. Followup ultrasonography of abnormal screening results, either from CA-125 testing or initial ultrasonography, were conducted by experienced sonographers.

The two screened groups were compared using cancer diagnoses identified through June 13, 2008. For this study, ovarian cancer cases included primary ovarian or fallopian tube cancer but excluded peritoneal cancer and ovarian tumors with uncertain behavior. Women were censored 1 year after their last CA-125 test or ultrasound. Repeat testing was required for 9.1 percent of women in the MMS group (or 8.7 percent; article contained a discrepancy) and 12.0 percent in the USS group. Overall, 1.0 percent of women underwent surgery, and 2.9 percent of women who had surgery but not cancer experienced a major complication (4.3 and 2.8 percent in MSS and USS groups, respectively). Major complications included perforation, hemorrhage requiring additional surgery, readmission, pulmonary embolism, deep-vein thrombosis, and infection. Surgeries varied significantly by group, with 0.2 percent of women undergoing surgery in the MMS group and 1.8 percent in the USS group.

The number of cancer cases detected was similar (42 in the MMS group and 45 in the USS group), although more borderline tumors were observed in the USS group (20 vs. 8 in the MMS group). For invasive cancer, the sensitivity, specificity, and PPV were 89.5, 99.8, and 35.1 percent, respectively, for the MMS group and 75.0, 98.2, and 2.8 percent for the USS group. For all cancer, including 28 borderline tumors, the corresponding numbers were 89.4, 99.8, and 43.3 percent in the MMS group, and 84.9, 98.2, and 5.3 percent in the USS group. Specificity was significantly higher in the MMS group, which is reflected in the higher PPV. Sensitivity was also higher for the MMS group compared with the USS group, although not significantly. Overall, 48.3 percent of the invasive cancer cases were early stage (Stage I or II), with no significant stage distribution difference between the two groups.

Despite the similar number of women randomized to each group, more women withdrew from the USS group (n=2,409) than from the MSS group (n=562). This largely seemed to be driven by a failure to keep three screening appointments (USS, n=757; MMS, n=72) or individuals changing their mind (USS, n=1,490; MMS, n=483). Randomization balanced known characteristics across the two screening groups and thus it is unclear why there was a substantial difference in withdrawals by screening group. It is possible that the different withdrawal rate reflects something about patient acceptability of annual transvaginal ultrasonography screening as the primary approach, although this is speculative.

In addition to being one of the few randomized, controlled trials of ovarian cancer screening, primary study results from UKCTOCS are eagerly awaited because they will provide information on the impact of more complicated screening algorithms, such as that used in the MMS group, on mortality. The high proportion of early-stage tumors detected is encouraging, although it should be noted that results have been presented from the baseline prevalence screening only and not yet compared with usual care. The proportion of early-stage tumors may decline in subsequent screening rounds, as the initial screening might be more likely to identify early-stage, slow-growing tumors than later screening cycles. However, the proportion of surgeries conducted after identifying a benign, instead of cancerous, mass may also decrease in subsequent screenings.

Trial recruitment is complete, with screening planned through December 31, 2011. Study participants will be followed for outcomes through December 31, 2014.[10,11] Based on this timeline, results may be available in 2015.

Shizuoka Cohort Study of Ovarian Cancer Screening

In 2008, Kobayashi et al described the impact of screening on stage at diagnosis using data from a randomized, controlled trial within the Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) in Japan.[9] Asymptomatic postmenopausal women (median age, 58 years [no age range provided]) who visited a hospital for a gynecologic examination between 1985 and 1999 were randomized to either a screening or control group. Screening was conducted by transvaginal and/or transabdominal ultrasonography (two-view) and serum CA-125 testing. If both tests were normal, screening was repeated a year later. If ultrasonography results were abnormal, women were referred for further evaluation, including a repeat scan prior to surgery. If only CA-125 levels were abnormal (>35 U/mL), women were rescreened at 6 months, apparently with both tests. The control group consisted of usual medical care.

Women were followed through December 31, 2002 for the development of epithelial ovarian cancer through SCSOCS and linkage with the Shizuoka Cancer Registry. The number of ovarian cancer cases detected was similar among the screening and control groups: 35 cases (27 screen-detected and eight outside the screening program) among 41,688 women in the screening group and 32 cases among 40,799 women in the control group. The authors found a nonstatistically significant shift toward an earlier stage at diagnosis among the screened group compared with the control group. Specifically, there were more Stage I cancer cases in the screened group (51 percent overall and 63 percent for screen-detected cancer) compared with the control group (38 percent). Correspondingly, there were fewer Stage III cancer cases (31 percent overall and 26 percent for screen-detected cancer in the screened group and 50 percent in the control group). However, an estimated 33 surgeries were required to detect each case of screen-detected cancer.

The average number of screening examinations was 5.4 during a mean followup of 9.2 years. Histologic type appeared to be somewhat different among cases in the screening versus control groups. In particular, serous tumors comprised about 31 percent of cases in the screened group and 50 percent among the control group. Potential reasons for this difference were not addressed in the article because the authors' assessment was that histology was similar across groups; case

numbers were relatively small in both groups. Mortality results were planned for a separate publication, although they do not appear to be available yet.

Results from this trial are difficult to interpret for several reasons. First, detection of cancer increased over the study period. The detection rate for the first screening test was 0.31 per 1,000 women and increased to 0.38–0.74 per 1,000 women in subsequent screenings. This increase is somewhat surprising, although it may reflect improvement in ultrasonography methods over the study period. Second, the detection rate overall may be low; as noted by Buys et al, the case numbers in SCSOCS were substantially lower than in the similarly sized PLCO Trial.[7] Third, the authors focused on comparisons between screen-detected cancer in the screened group and all cancer in the control group, rather than simply comparing the two groups as randomized (i.e., using all cancer in both groups). Fourth, the article omitted details which would help the reader interpret the findings. For instance, a statement regarding whether it is routine for women to obtain gynecologic examinations at hospitals in Japan would help the reader assess whether the study population represented the general population or a select population. Also, while the authors stated that transvaginal ultrasonography has been used in Japan "predominantly since 1990," the frequency of use in the study was not quantified. Additionally, it was unclear how exclusion criteria were applied. For instance, the authors stated that individuals who had cancer "diagnosed at any time before registration" were excluded. However, only 14 cases of cancer were excluded among this older population (median age, 58 years), and later the article refers to the exclusion of individuals with "subsequent diagnosis of malignant disease." Thus, it seems possible that individuals with cancer diagnosed before baseline were excluded only if the diagnosis occurred between the invitation to participate in the trial and randomization. The analysis methods were also unclear (e.g., conditional multiple logistic regression was mentioned in this unmatched study, which did not present relative risks). Given the limited data from randomized trials on ovarian cancer screening, it is hoped that the mortality results will be published with additional details about the trial methods.

Limitation of This Review

As noted in the previous evidence review, the search strategy employed for this review was designed to identify substantial new studies, particularly randomized trials, published in indexed journals. Thus, this is not a comprehensive review of the literature.

Emerging Issues and Research Gaps

Clinicians and researchers continue to seek ways to improve the performance and effectiveness of ovarian cancer screening strategies. First, improvement of the tests themselves are being sought through identification of panels of markers (including proteomics studies) and evaluation of different imaging techniques or scoring systems. Second, combinations of tests are being used to try to increase performance characteristics of screening tests or screening algorithms, such as screening concurrently or sequentially with CA-125 testing and ultrasonography. More complex information, such as CA-125 trajectory instead of absolute value, is also being evaluated to improve screening. Third, efforts have been made to identify a higher-prevalence population in

whom the risk-benefit ratio of screening may be shifted through the increased prevalence of the population. These efforts have included developments of symptom indices to be used as a first step in "screening" women who are not asymptomatic. Fourth, some have proposed alterations to the followup procedures, such as followup by imaging surveillance rather than invasive surgery, which alters the risk-benefit ratio.[12,13]

Given that UKCTOCS results will not be available for several years and it is unclear when SCSOCS results will be released, it seems unlikely that substantial new evidence will be available in the next few years regarding the impact of ovarian cancer screening on mortality. However, if there were a radical shift in the screening tests themselves or in the interpretation or application of them (e.g., screening tests used in combination with risk prediction models), the USPSTF may wish to take a look at the evidence prior to the publication of the trial results.

Despite the lack of evidence or recommendations in support of ovarian cancer screening, a recent survey of physicians reported frequent screening for ovarian cancer (transvaginal ultrasonography or CA-125 testing) in hypothetical cases.[14] Vignettes of women with varied characteristics (e.g., age, race, insurance coverage, and ovarian cancer risk as determined by family history and presence of *BRCA* mutations) were evaluated by 1,574 physicians, including both primary care clinicians (family physicians and general internists) and specialists (obstetrician-gynecologists). In these hypothetical situations, 65.4 percent of physicians reported use of ovarian cancer screening tests "sometimes" or "almost always" for medium-risk women, with 24 percent responding "almost always" use; medium-risk women were defined as those with a 4–5 percent lifetime risk based on maternal history of ovarian cancer death. Similarly, 28.5 percent of physicians reported "sometimes" or "almost always" using ovarian cancer screening tests among low-risk women, with 6.3 percent reporting "almost always" use; low-risk women were operationalized as women with a maternal history of breast cancer (1.5 percent lifetime ovarian cancer risk). For both risk groups, if the patient in the scenario requested ovarian cancer screening, physicians were more likely to report offering screening than if the patient did not. Approximately half of physicians listed the USPSTF among the top three organizations influencing their cancer screening recommendations, and compliance with screening recommendations was higher among these physicians. This survey highlights both the frequently reported use of ovarian cancer screening among low- and medium-risk women and the influence of USPSTF screening recommendations in guiding clinical practice.

Recommendations From Other Groups

The USPSTF recommendations are consistent with guidelines from other professional societies in the United States, although other organizations tend to simply state that screening for ovarian cancer is not recommended rather than explicitly weighing the potential benefits and harms.

In 2006, the American Congress of Obstetricians and Gynecologists published a Committee Opinion stating that "currently, there are no effective techniques for the routine screening of asymptomatic, low-risk women for ovarian cancer."[15] In "Cancer Facts & Figures 2011," the American Cancer Society included a table of recommended screening tests for average-risk asymptomatic women, with no mention of ovarian cancer. In a section specifically on ovarian

cancer, it states that there is "currently no sufficiently accurate screening test" for ovarian cancer.[1]

Similar conclusions have been reached by professional societies in other countries. In 2009, the National Breast and Ovarian Cancer Centre issued a position statement following a meeting with key Australian stakeholders concluding that evidence did not support population-based screening for ovarian cancer among asymptomatic women.[16] The position statement was subsequently endorsed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Royal Australian College of General Practitioners, the Australian Society Gynaecologic Oncologists, Cancer Council Australia, and the Screening Subcommittee of the Department of Health and Ageing.

Conclusions

Three randomized, controlled trials on ovarian cancer screening were published during the search period, only one of which presented mortality results. The results are consistent with the current USPSTF guidelines for ovarian cancer screening among asymptomatic, average-risk women.

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